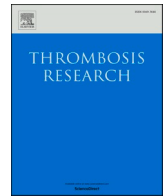


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Every 6 seconds in Europe

Every 6 seconds, a woman gives birth in Europe, or in North America. Every 6 seconds, a woman faces the increased risk of venous thromboembolism (VTE) in the postpartum period. And for each of these women, care practitioners are struggling to decide, if the benefit of providing heparin thromboprophylaxis to prevent postpartum VTE outweighs the potential risks and costs.

Given the 5.3 million annual births in geographical Europe, and the 140 million annual births worldwide, pregnancy-related VTE possesses a huge relevance from a public health's perspective and substantially impacts maternal health. It is responsible for about 10% of maternal deaths [1], lowers long-term quality-of-life and obliges for several months of therapeutic anticoagulation with its associated constraints and bleeding episodes. Most practitioners would agree that preventing maternal VTE is highly desirable, but the incidence of acute PE among pregnancy-related hospitalization has not been decreasing recently in the United States, including that of high-risk PE [2]. In contrast to the antenatal period, with a constant or gradually increasing risk over 9 months, the postpartum period represents the low hanging fruit here, with the highest VTE risk in the 3 first weeks after delivery [3] and no risk of thromboprophylaxis for the newborn.

Unfortunately, we suffer from a paucity of high-quality data to guide clinical practices for postpartum thromboprophylactic regimens. Whereas large-scale placebo-controlled randomized trials have established the benefit of short-term thromboprophylaxis in surgical and medical patients over the last 30 years, guidance documents to inform thromboprophylactic strategies in postpartum women are still based on small non-informative studies (often without an adequate comparator) or mostly expert opinions. And although various international guidelines (ACCP, RCOG, ASH, ACOG, etc.) advise the use of thromboprophylaxis in women depending on their thrombotic risk factors, they differ widely in the proportion of suggested use of thromboprophylaxis, ranging from 9 to 40% of postpartum women [4], reflecting the underlying lack of solid evidence.

In this context, Lu Ban et al. add an interesting piece with the aim to help, inform and improve the scientific rigor to current practices: they present an external retrospective validation of a risk assessment model (RAM) of postpartum VTE [5]. Traditionally, VTE RAM combine risk factors to separate patients at "high" risk of VTE from those at "low" risk of VTE. Well-known examples include the Improve RAM, the Padua RAM and the Geneva RAM, which identify low-risk and high-risk acutely-ill medical inpatients with 3-month VTE risks <1% and >1–3%, respectively [6], and are used in daily clinical practice to guide the use of in-hospital thromboprophylaxis. Here, the Maternity Clot Risk RAM is a complex equation of several maternal factors (varicose veins, BMI, age, co-morbidities, smoking) and obstetrical risk factors (pre-

eclampsia, postpartum hemorrhage, postpartum infection, delivery method, parity, infant birth weight), with variables in polynomial and logarithmic forms. It has been developed by the same group, using the Clinical Practice Research Datalink, a longitudinal UK primary care database [7].

In this validation, the authors use another database of UK primary care database (QResearch) to test the RAM in a cohort of 535,583 women aged <60 years with 700,185 deliveries, between 2004 and 2015. The average risk of postpartum VTE was 8 per 10,000, or 1 in 1250 women, without further details on the type of VTE or its timing in the postpartum period. Compared with the development and initial validation study [7], this external validation had a fair but slightly poorer discrimination (C-statistic of 0.67, compared with 0.70–0.73) and calibration, with an overestimation of risks in high-risk women. Very few women had predicted VTE risk >0.2% (5%) or >1% (0.1%). Decision curve analyses suggest a benefit of the RAM against current UK practices, but it remained marginal: using the RAM instead of the RCOG guidelines to guide the use of thromboprophylaxis to the 36% of women at most risk would only increase the sensitivity from 57% to 59%, translating into a potential reduction of 2% of all VTE events.

At this point, should we integrate the Maternity Clot Risk in clinical practice? This validation analysis is statistically transparent and sound, but the data suffer from potential bias and misclassification that are acknowledged by the authors. First, VTE events were not individually adjudicated. The researchers used a combination of VTE codes with some record of anticoagulation, based on an old validation study of mostly inpatient VTE among non-pregnant women showing a positive predictive value of 84%. The true validity of the VTE events in the current sample is therefore questionable. Second, the lack of data on postpartum thromboprophylaxis is problematic, bringing distortions to associations of risk factors with VTE and to the observed absolute VTE risks. Third, bias may also arise from misclassification of important risk factors and some missing details such as body-mass index or the prevalence of thrombophilia. Given these limitations, we feel that a general use of the Maternity Clot Risk RAM cannot be recommended at present, every 6 seconds in Europe, until further validity research has been performed.

We agree with the authors that this RAM may add some flexibility, with thromboprophylactic strategies tailored to individual risk thresholds in the future. These thresholds remain highly uncertain: while experts have advised thresholds of postpartum VTE of 1–3% [8], current guidelines are likely using thresholds of 0.1–0.2% [4], and women's preferences have not been specifically explored. In addition to highly individual VTE risks, the burden of thromboprophylaxis is a major and highly subjective factor in the decision process, and solid risk

<https://doi.org/10.1016/j.thromres.2021.07.012>

Received 23 June 2021; Received in revised form 18 July 2021; Accepted 19 July 2021

Available online 21 July 2021

0049-3848/© 2021 Published by Elsevier Ltd.

assessments for thromboprophylaxis-related bleeding are lacking in pregnancy and post-partum. Preferences are important here, as among women with previous VTE, 26% say they are not willing to take antenatal LMWH in spite of an estimated 5–7.5% risk of pregnancy-associated VTE [9], and adherence to thromboprophylaxis in pregnancy is lower in the postpartum than in the antenatal period [10].

Taken together, the Maternity Clot Risk RAM may prove to be an important piece in the puzzle of postpartum VTE. However, in 2021, the true effectiveness and safety of postpartum thromboprophylaxis and its acceptance by women are still areas of uncertainty and deserve ambitious research efforts, such as the current pilot PARTUM randomized trial (NCT04153760) of aspirin and similar trials for LMWH.

Declaration of competing interest

None.

Acknowledgments

No funding was received for this editorial.

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